REMARKS

Status

Applicants and their representatives thank Examiner Duffy for the courtesy extended during telephone interviews on May 12 and May 23, 2006. Amendments to the specification and claims are now presented as discussed in the interviews.

Applicants have canceled claims 1, 4, 7-11, 15, 21, 28, 30, 31, 34, 37, 41, 44, 48, and 51; amended claims 19, 20, 25-27, 29, 32, 33, 35, 36, 38-40, 42, 43, 45-47, 49, 50, and 52; and added new claims 53-56. Support for the amendments and new claims can be found, e.g., at page 3, lines 25-29 (SEQ ID NO:9 is the amino acid sequence of human BAFF); page 3, line 30, through page 4, line 2 (B-cell growth or immunoglobulin production); page 4, lines 14 to 23 (fusions to heterologous amino acid sequences, e.g., the Tc region of an immunoglobulin); page 5, lines 2-6 (nucleic acid residues 240-341 of SEQ ID NO:2 correspond to amino acids 8-41 of SEQ ID NO:1, thus "potential transmembrane region at nucleic acid residues 375-459 of SEQ ID NO:2" corresponds to amino acids 53 to 81 of SEQ ID NO:1); page 7, lines 23-25 (BAFF-R [BCMA] ECD may comprise amino acids 8-41 or 1-51 of SEQ ID NO:1); and page 8, lines 3-11 (an active BAFF-R [BCMA] polypeptide that is at least 95% identical to a BAFF-R ECD sequence).

The specification and sequence listing have been amended to provide the sequence of BAFF, as suggested by the Examiner. Support for these amendments can

be found at page 3, lines 28-29, which discloses that "BAFF is the same molecule previously described in WO/9912964, which is incorporated by reference herein."

Applicants respectfully request entry of these amendments under 37 C.F.R. § 1.116. The proposed amendments (1) do not raise new issues or necessitate additional searches and (2) place the application in condition for allowance or in better form for appeal. Applicants respectfully submit that this amendment should allow immediate action by the Examiner.

Written Description

The Examiner maintains the written description rejection under 35 U.S.C. § 112, first paragraph. The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See Vas-Cath, Inc. v. Mahurkar,* 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991). The Examiner contends that the specification does not provide an adequate description of (1) fusions to heterologous amino acid sequences; (2) inhibition of B-cell expression or immunoglobulin expression; (3) fragments of amino acids 1 to 51 of SEQ ID NO:1; or (4) sequences that bind to BAFF and are 80-90% identical to amino acids 1 to 51 or 8 to 41 of SEQ ID NO:1.

Applicants submit that the amended claims are fully supported by the specification. First, Applicants note that support for fusions to heterologous amino acid

sequences can be found, e.g., at page 4, lines 14 to 23. Second, Applicants' proposed claim amendments replace "B-cell expression or immunoglobulin expression, or both" with "B-cell growth or immunoglobulin production, or both" (for support, see page 3, line 30, to page 4, line 2). Third, the amended claims do not refer to fragments of amino acids 1 to 51 of SEQ ID NO:1.

Finally, the amended claims relate to BCMA polypeptides that bind to a BAFF polypeptide as set forth in SEQ ID NO:9 and that are at least 95% identical to amino acids 1 to 51 or 8 to 41 of SEQ ID NO:1. This language satisfies the written description standard for sequence variants articulated in Example 14 of the Written Description Guidelines. Example 14 states that disclosure of a single protein sequence provides adequate written description for the genus of proteins comprising sequences that are at least 95% identical to that sequence and catalyze the reaction of A to B. As in Example 14, the instant claims relate to a polypeptide comprising an amino acid sequence that satisfies a functional limitation (binding to BAFF) and is at least 95% identical to a disclosed sequence (amino acids 8 to 41 or 1 to 51 of SEQ ID NO:1). As in Example 14, the specification and knowledge in the art provide procedures for making variants of the disclosed sequence and assays to identify variants satisfying the functional limitation. See, e.g., Bowie et al. (previously submitted); Fersht (previously submitted); and Examples 1-4, pages 17-21.

In short, Applicants' disclosure, considered in view of knowledge in the art, satisfies the written description standard articulated by the Federal Circuit in *Vas-Cath, Inc. v. Mahurkar* and by the PTO in the Written Description Guidelines. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Enablement

The Examiner maintains the enablement rejection under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claims. While acknowledging enablement of a pharmaceutical composition comprising a polypeptide comprising residues 1-51 of SEQ ID NO:1 that binds to BAFF, the Examiner alleges that the specification does not enable a pharmaceutical composition comprising a polypeptide comprising residues 8-41 of SEQ ID NO:1 or an amino acid sequence that binds to BAFF and is at least 80, 85, or 90% identical to residues 1-51 or 8-41.

Applicants respectfully submit that the amended claims are fully enabled by the specification. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). As discussed above with respect to written description, the amended claims relate to polypeptides that bind to BAFF and comprise an amino acid sequence that is at least 95% identical to amino acids 8-41 or 1-51 of SEQ ID NO:1. Again, the Examiner has acknowledged enablement of a pharmaceutical composition

comprising a polypeptide comprising residues 1-51. Applicants respectfully submit that the specification also enables polypeptides comprising residues 8-41. Under *In re Angstadt*, the Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. The Examiner has not met that burden here. The Examiner's observation that "there is no activity demonstrated for the peptide of residues 8-41 of SEQ ID NO:1" (*Final Office Action*, at 8) is not a reason that the specification is not enabling. "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). Applicants demonstrate that a polypeptide comprising amino acids 1-51 binds BAFF (page 5, lines 7-10; pages 20-21). The specification also teaches that amino acids 8-41 constitute the cysteine rich domain. Page 5, lines 2-5. As discussed by Smith et al., the cysteine rich domain is "the canonical motif" of the TNF receptor superfamily. *Cell* 76:959-962 (1994) (attached). In light of Applicants' demonstration that BCMA is a receptor for BAFF and that BAFF-binding activity is localized within amino acids 1-51, the skilled artisan would expect the canonical cysteine rich domain to bind BAFF. The Examiner has offered no reason to doubt this expectation. Viewed in light of all the facts, the absence of a working example of amino acids 8-41 is insufficient to meet the Examiner's burden under *In re Angstadt*.

Applicants submit that the specification also provides enabling support for pharmaceutical compositions comprising polypeptides that bind to BAFF and are at least 95% identical to residues 1-51 or 8-41 of SEQ ID NO:1. Again, the test for enablement is whether any necessary experimentation is undue. *In re Angstadt.* The possibility that compounds satisfying a structural limitation may fail to fulfill a functional limitation does not prove lack of enablement. "Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." *Id.* at 219. As Applicants discussed in the reply of July 18, 2005, it was understood in the art that while generating sequence variants retaining biological activity might require some experimentation, any such experimentation would not be undue. Bowie et al. demonstrates that methods for systematically generating and testing variants were well known in the art. Bowie et al., *Science* 247:1306-1310 (1990) (previously submitted). Bowie et al. teaches that even following this systematic approach, without any guidance as to which variants would likely retain biological activity, the skilled artisan would expect to generate functional variants with only routine experimentation, since "proteins are surprisingly tolerant of amino acid substitutions."

Despite the Examiner's assertion to the contrary, Bowie et al. does not require "comparison of sequences to discover how a protein folds and how it performs its functions or determination of a particular structure of a polypeptide." *Final Office*

Action, at 7. In the particular set of experiments discussed in Applicants' reply of July 18, 2005, the approximately 1500 single amino acid substitutions tested in the *lac* repressor were chosen simply on the basis of available genetic techniques; the researchers did not rely on any comparison to other sequences. Bowie et al. at 1306, col. 2, lines 14-17 (citing Miller et al., *J. Mol. Biol.* 131:191-222 (1979) (attached)).

In the instant case, the skilled artisan would have even higher expectations for success than one would have in applying Bowie et al.'s systematic approach. The specification and knowledge in the art provide ample guidance as to changes that could likely be made to the sequence without disrupting activity. As Applicants previously noted in the reply of July 18, 2005, general guidelines for producing variants likely to retain activity were known in the art. *See* Ferscht, *Structure and Mechanism in Protein Science* 425 (1999) (previously submitted). Applicants' disclosure, combined with knowledge in the art, also provided guidance specific to BCMA. The specification discloses that BCMA may be isolated from a variety of sources, including murine or human tissue. Page 7, lines 7-9. In fact, both the human and mouse BCMA sequences were known at the time. See Madry et al., *International Immunology* 10:1693-1702 (1998) (submitted with IDS of November 14, 2002). Thus, although Bowie et al. indicates that the skilled artisan could expect success even if unable to predict *a priori* which sequence variants would retain the functional limitation, here, where the artisan could make such predictions, the expectation of success would be even higher. As

noted by Madry et al., comparing the mouse and human sequences allows the skilled artisan to "define the conserved regions and . . . identify any significant functional motif." *Id.* at 1698. Amino acids that are conserved between the homologs are more likely to be important for BAFF binding. Conversely, amino acids that vary between the mouse and human sequences indicate regions of the polypeptide that are more likely to tolerate variation from SEQ ID NO:1. The specification also teaches that conservative substitutions are likely to preserve activity. Page 17, lines 3-10. Following these guidelines, the skilled artisan would expect to identify functional variants through no more than routine effort.

In summary, Applicants' disclosure, considered in view of knowledge in the art, satisfies the enablement standard articulated by *In re Angstadt.* Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Definiteness

The Examiner has rejected the claims under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner states that the limitation, "effective to inhibit B-cell expression or immunoglobulin expression, or both," prevents the skilled artisan from readily ascertaining the metes and bounds of the pharmaceutical composition. The amended claims overcome this rejection by replacing "B-cell expression or immunoglobulin expression" with "B-cell growth or immunoglobulin production."

The Examiner also states that claims 32-38 are *prima facie* indefinite because the phrase "the transmembrane domain of BCMA" lacks antecedent basis in the claims. The amended claims overcome this rejection by replacing "the transmembrane domain of BCMA" with "amino acids 53 to 81 of SEQ ID NO:1." Support for this amendment can be found at page 7, lines 19-20 ("essentially free of transmembrane and cytoplasmic domains") and page 5, lines 2-6 (nucleic acid residues 240-341 of SEQ ID NO:2 correspond to amino acids 8-41 of SEQ ID NO:1, thus the "potential transmembrane region at nucleic acid residues 375-459 of SEQ ID NO:2" corresponds to amino acids 53 to 81 of SEQ ID NO:1).

In view of these amendments, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Priority

The Examiner has rejected Applicants' claim for domestic priority to 60/149,378, 60/181,684, and 60/183,536. The Examiner states that the priority applications fail to adequately describe and enable the claimed pharmaceutical compositions.

Without conceding the Examiner's position with respect to the previously pending claims, Applicants respectfully submit that the amended claims are entitled to the priority of 60/149,378 (filed August 17, 1999).

Application Serial No. 60/149,378 demonstrates to the skilled artisan that Applicants had possession of the claimed invention at least as of August 17, 1999.

Support for each element of the amended claims can be found in the specification. For example, page 15, line 26, to page 16, line 7, discloses pharmaceutical compositions comprising a BAFF-R [BCMA] polypeptide. Page 15, lines 17-19, discloses use of a BCMA polypeptide to inhibit B-cell growth or immunoglobulin production, or both. Page 11, lines 18-19, discloses "peptides derived from BAFF-R which have the ability to bind to BAFF." Page 4, lines 3-4, discloses that "BAFF is the same molecule previously described in WO/9912964, which is incorporated by reference herein." Page 7, line 30, to page 8, line 7, discloses "an active BAFF-R" having at least about 80, 85, 90, or 95% sequence identity with SEQ ID NO:1 for a full-length BAFF-R or a BAFF-R ECD sequence. Page 6, lines 8-11, discloses the BAFF-R-Fc construct used in Example 4 (pages 19-21), which comprises nucleic acids 1-153 of BAFF-R; the resulting protein thus comprises amino acids 1-51 of BCMA (SEQ ID NO:1). Page 7, line 23, discloses a BAFF-R ECD comprising amino acids 8-41 of SEQ ID NO:1. Page 7, lines 19-20, discloses that BAFF-R ECD is essentially free of transmembrane and cytoplasmic domains of BAFF-R. Page 6, lines 3-7, discloses that nucleic acid residues 240-341 of SEQ ID NO:2 correspond to amino acids 8-41 of SEQ ID NO:1, the "potential transmembrane region at nucleic acid residues 375-459 of SEQ ID NO:2" thus corresponds to amino acids 53 to 81 of SEQ ID NO:1. Example 5 (page 21, lines 6-24) describes the "generation of soluble receptor forms." Page 5, lines 11-14 discloses

fusions to a "heterologous polypeptide or amino acid sequence," e.g., an "Fc region of an immunoglobulin."

Applicants respectfully submit that Application Serial No. 60/149,378 fully enables the claimed pharmaceutical compositions. As discussed above, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). Under *In re Angstadt*, the Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. The Examiner's contention that the priority document fails to demonstrate any activity *in vivo* or to provide a nexus between *in vitro* and *in vivo* data fails to meet the burden established by *In re Angstadt*.

Applicants respectfully submit that 60/149,378, viewed in light of the state of the art at the time it was filed, does establish a nexus between the *in vitro* data disclosed in the application and *in vivo* use of the claimed pharmaceutical compositions; this nexus renders *in vivo* data unnecessary for enablement. An *in vitro* example constitutes a "working example" if that example "correlates" with the claimed invention. MPEP § 2164.02. The burden is on the Examiner to give reasons for a conclusion of lack of correlation. *Id.* Only a "reasonable correlation" is required between *in vitro* data and *in vivo* use; "a rigorous correlation is not necessary." *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). The Examiner has offered no reason

to conclude that correlation is lacking between the *in vitro* data in 60/149,378 and *in vivo* use of the claimed pharmaceutical compositions. Indeed, Applicants' disclosure and the state of the art at the time demonstrate that the skilled artisan would perceive a reasonable correlation. The skilled artisan would consider at least the following:

- BAFF was known to costimulate B-cell proliferation and immunoglobulin secretion. *See* Schneider et al., *J. Exp. Med.* 189:1747-1756 (June 7, 1999) (attached).
- Soluble forms of receptors in the TNF family (comprising, e.g., the extracellular domain fused to an Fc domain) were known to known to be effective inhibitors of ligand-receptor signaling *in vivo*. *See, e.g.*, Moreland et al., *Ann. Intern. Med.* 130:478-486 (March 16, 1999) (attached).
- Examples 1-3 demonstrate that BAFF binds to BCMA-transfected cells (but not control cells).
- Example 4 demonstrates that BAFF binds to a fusion protein comprising amino acids 1-51 of BCMA and the Fc domain of human IgG1.

Applicants' *in vitro* data demonstrating that BCMA binds BAFF and that amino acids 1-51 suffice for BAFF-binding, taken in view of BAFF's costimulatory activity and the general ability of soluble TNFRs to inhibit signaling *in vivo*, would lead the skilled artisan to conclude that the claimed pharmaceutical compositions could be used *in vivo* without undue experimentation.

In view of these amendments and remarks, Applicants submit that priority application 60/149,378 both describes and enables the claimed invention. Accordingly, Applicants request that the Examiner reconsider the priority claim and grant priority to August 17, 1999.

Novelty

The Examiner has rejected claims 19-21 and 26-52 under 35 U.S.C. §102(b) and claim 25 under 35 U.S.C. §102(a) as allegedly anticipated by WO/00/40716 ("the '716 application"). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the priority date of August 17, 1999. Thus, without comment as to the alleged anticipation of the amended claims by the teachings of the '716 application, Applicants submit that the instant application predates the reference, which is only effective as of its July 13, 2000, publication date.

The Examiner has rejected claims 19-21 and 25-52 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,475,987 ("the '987 patent"). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the priority date of August 17, 1999. Thus, without comment as to the allegation that the claims read on the teachings of the '987 patent, Applicants submit that the instant application predates the reference, which issued November 5, 2002 and was filed May 5, 2000 (without acquiescing as to the priority date to which the '987 patent is entitled, Applicants note that the Examiner states that this reference has the

benefit of priority to May 1, 2000). Accordingly, Applicants respectfully request that the rejection over the '987 patent be withdrawn.

The Examiner has also rejected claims 19-21 and 25-52 under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent Application Publication 2003/0148445 ("the '445 application"). In view of the foregoing remarks with respect to priority, Applicants submit that the instant application is entitled to the priority date of August 17, 1999. Thus, without comment as to the allegation that the claims read on the teachings of the '445 application, Applicants submit that the instant application predates the reference, which was published on August 7, 2003 and was filed August 9, 2002 (without acquiescing as to the priority date to which the '445 application is entitled, Applicants note that the Examiner states that this reference has the benefit of priority to May 1, 2000). Accordingly, Applicants respectfully request that the rejection over the '445 application be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that all outstanding rejections have been overcome. Accordingly, reconsideration of claims and expedited allowance are earnestly requested. The Examiner is urged to call the undersigned with any questions at (617) 452-1669.

Applicants believe that any fee required for the entry of this amendment is accounted for by the accompanying Petition for Extension of Time and Request for

Continued Examination. However, in the event of an error, please grant any additional extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 14, 2006

By: _____
Nathaniel S. Edwards
Reg. No. 57,745